

Species Differences in Affinity and Efficacy of Carbachol for Ileal Muscarinic Receptors

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The muscarinic effects of carbachol were compared on the isolated ileums of guinea-pig, rat and rabbit to elucidate the underlying mechanism of species differences in sensitivity for carbachol. The ED_{50} value estimated on the guinea-pig ileum was 4 to 6-fold lower than those obtained on the rat and rabbit ileums, but the K_A values of carbachol determined by functional assays were almost identical with 12~17 μ M in all of three ileums. The competition data of carbachol for [3 H]QNB binding were best described by a two-site model, yielding the K_i values of 0.4~0.6 μ M and 12~16 μ M for high(K_H) and low(K_L) affinity sites, respectively. The low affinity dissociation constants(K_L) of carbachol determined from receptor binding studies thus were not significantly different from the K_A values estimated from functional studies. The percentage of receptor occupation that carbachol requires for half-maximal response was approximately 3 to 5-fold lower in guinea-pig compared to rat and rabbit, whereas the density of muscarinic binding sites per gram of ileum measured by [3 H]QNB saturation isotherms was two-fold higher in guinea-pig than that in rat and rabbit. Therefore, the numbers of muscarinic receptors occupied at ED_{50} values of carbachol were about two-fold lower in guinea-pig, suggesting two-fold greater intrinsic efficacy. These results indicate that the guinea-pig ileum has higher muscarinic receptor density and greater intrinsic efficacy for carbachol than the rat and rabbit ileums.